"FORMULATION, DEVELOPMENT AND EVALUATION OF NANOSTRUCTURED LIPID CARRIER FOR ORAL DRUG DELIVERY SYSTEM"

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Submitted

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1. Abstract of proposed work plan/ problem:

The drug delivery system enables the release of the active pharmaceutical ingredient to achieve a desired therapeutic response. Conventional drug delivery systems (tablets, capsules, syrups, ointments, etc.) suffer from problems like poor bioavailability at target site, high dose dumping, and fluctuations in plasma drug level and are unable to achieve sustained release. Without an efficient delivery mechanism, the whole therapeutic process can be rendered useless. During the recent years, more attentions have been focused on lipid base drug delivery system (liposome, aquasomes, niosome, phytosome, microspheres, pharmacosomes, and solid lipid nanoparticle, nano-structured lipid carrier) to overcome some limitations of conventional formulations. The solid lipid nanoparticle (SLN) are made of solid lipid material, which remains in the solid state at room temperature, protects the chemically labile drugs, and provides slow drug release to achieve controlled drug release profiles for prolonged time intervals. Nanostructured lipid carrier (NLC) is second generation smarter drug carrier system having solid matrix which is made up of physiological, biodegradable and biocompatible lipid materials, surfactants etc. The physiochemical diversity and biocompatibility of lipids and their ability to enhance oral bioavailability of drugs have made lipid nanostructured lipid carrier very attractive for oral drug delivery. Moreover, the lipid-based formulations can positively influence drug absorption in a number of ways including; increasing solubilization capacity, preventing drug precipitation on intestinal dilution, enhancing permeability. From the literature survey it is found that, number of available drugs has poor solubility & bioavailability issues regarding conventional form, so it is required to develop NLCs. NLCs have been proved as one of the beneficial systems for oral administration of poorly water soluble drugs having low bioavailability. Drugs containing nanostructured lipid carrier will be prepared by using homogenization technique or solvent injection or double emulsification method or microemulsion formation techniques or sonication etc. Nano-structured lipid carrier formulation will be evaluated and optimized by using various physicochemical parameters like particle size, SEM, DSC, FTIR, Zeta potential, entrapment efficiency, drug content, In-vitro, In-vivo study and stability studies.

Key words: - Solid lipid nanoparticle, Nanostructured lipid carrier, oral drug delivery, bioavailability.

2. Introduction:

Over the last 20 years, nanotechnology has practically made its influence in all technical fields, including pharmaceutics. Industry estimated that approximately 40% of lipophilic drug candidates fail due to solubility and formulation stability issues, which has been solved by various novel and advanced lipophilic drug delivery technologies. The lipids employed to prepare lipid nanoparticles are usually physiological lipids with low acute and chronic toxicity.

In recent years, solid lipid nanoparticles (SLNs) have garnered great importance as potential drug carriers for oral delivery due to their unique advantages and great versatility as compared to polymeric nanoparticles, nanoemulsions, liposomes. The SLNs are made of solid lipid material, which remains in the solid state at room temperature, protects the chemically labile drugs, and provides slow drug release to achieve controlled drug release profiles for prolonged time intervals. Nanostructured lipid carrier (NLC) is second generation smarter drug carrier system having solid matrix at room temperature. This carrier system is made up of physiological, biodegradable and biocompatible lipid materials, surfactants and is accepted by regulatory authorities for application in different drug delivery systems. NLC exhibit superior advantages over other colloidal carriers like nanoemulsions, polymeric nanoparticles, liposomes, SLN etc. and thus, have been explored to more extent in pharmaceutical technology. The whole set of unique advantages such as enhanced drug loading capacity, prevention of drug explosion leads to more flexibility for modulation of drug release and makes NLC versatile delivery system for various routes of administration. NLC has pharmaceutical applications for the various routes of drug delivery like topical, oral, pulmonary, ocular and parenteral administration and its future perspective as a pharmaceutical carrier.

Oral administration is the most popular and patient-compliant route because it is minimally invasive, painless, it does not need trained personnel and it is cost-effective. In addition, oral administration can be implemented in systemic and local treatments. Along with these benefits, orally administrated drugs face physiological barriers that affect their bioavailability. Various studies have proven that this nanoplatform has shown improvement in oral bioavailability of drugs via promoting their intestinal absorption. This system has also shed a

light of hope for treatment of chronic diseases due to its modulation with drug efficacy and sustained for longer periods.

The physiochemical diversity and biocompatibility of lipids and their ability to enhance oral bioavailability of drugs have made nanostructured lipid carrier very attractive carriers for oral drug delivery. Moreover, the lipid-based formulations can positively influence drug absorption in a number of ways including; increasing solubilization capacity, preventing drug precipitation on intestinal dilution, enhancing membrane permeability, inhibiting efflux transporters, reducing CYP enzymes, enhancing chylomicron production and lymphatic transport.

NLCs have been proved as one of the beneficial systems for oral administration of poorly water soluble drugs having low bioavailability. Another important feature is the high dispersivity of NLCs due to which they exhibit a high specific surface area for enzymatic attack by intestinal lipases. Other advantages of giving NLC in oral forms include increased drug loading, improved drug inclusion, patient compliance, high particle concentration and cream like consistency of the carrier. The mechanisms involved in the absorption of the NLC from the intestine include direct uptake through the GI tract, increase in permeability by surfactants and decreased degradation and clearance. Besides this, the NLCs can also adhere on to the gut wall prolonging the residence time, and consequently the absorption.

Advantages of NLCs:

- NLCs provide an advantage of the control / target drug release.
- They help to improve the stability of pharmaceuticals.
- NLCs enhance drug solubility and the possibility of both hydrophilic and lipophilic drug incorporation.
- They enhance dispersability in an aqueous medium.
- NLCs have excellent biocompatibility.
- NLCs help in prevention of drug explosion.
- They provide an advantage of greater and higher drug content delivery.
- NLCs provide an advanced and efficient carrier system in particular for lipophilic substances.
- Incorporation of drug into lipid matrix, protects drug during In-vitro & In vivo study till reaching site of action

- They extend the release of the drug.
- The minute size of the lipid particles ensures close contact to the stratum corneum thus enhancing drug penetration into the mucosa or skin.
- NLCs provide higher drug loading, faster release rate and storage stability due to a use of blend of solid lipid and liquid lipid in their formulations.
- One of the carrier of choice for topically applied drugs because their lipid components have an approved status or are excipients used in commercially available topical cosmetic or pharmaceutical preparations.
- NLCs can strongly immobilize drugs and prevent the particle from coalescing by virtue of the lipid matrix compared to emulsions.

Components of NLC Drug Delivery System:-

The primary component of nanostructured lipid carriers that govern drug loading capacity, prolong action and stability of the formulations is lipid. Solid lipids like fatty acids, triglyceride, diglyceride, monoglyceride, steroids and waxes have been used for formulating NLC.

Solid lipids	Stearic acid, Cholesterol, Palmitic acid, Glyceryl monostearate, Cetylpalmitate, Glycerol behenate, Glycerol palmitostearate, etc
Liquid lipids	Castor oil, Palm oil, Coconut oil, Oleic acid, Soy bean oil, Almond oil, Caraway essential oil, etc
Surfactants	Phospholipids: Soy lecithin, egg lecithin and phosphatidyl choline, etc Ethyleneoxide/propylene oxide copolymers: Poloxamer 188, poloxamer 182, poloxamer 407 and poloxamine 908, etc. Sorbitanethyleneoxide/propyleneoxide copolymers: Polysorbate 20, polysorbate 60 and polysorbate 80, etc. Alkylarylpolyetheralcohol polymers: Tyloxapol, etc. Bile salts: Sodium cholate, sodium glycolcholate, sodium taurocholate and sodium taurodeoxycholate, etc. Alcohols: Ethanol and butanol, etc.

3. Review of Literature and Development in the subject (Previous work done in the relevant area):

Khaled M Hosny *et al.*, (2022) this article summarize the development of a nanostructured lipid carrier (NLC) of sesame oil (SO) loaded with miconazole (MZ) that could overcome the solubility problems of MZ and enhance its antifungal activity against oral candidiasis. In the formulation of this study, SO was used as a component of a liquid lipid that showed an improved antifungal effect of MZ. An optimized MZ-loaded NLC of SO (MZ-SO NLC) was used, based on a central composite design-based experimental design; the particle size, dissolution efficiency, and inhibition zone against oral candidiasis were chosen as dependent variables. A software analysis provided an optimized MZ-SO NLC with a particle size of 92 nm, dissolution efficiency of 88%, and inhibition zone of 29 mm. Concurrently, the *ex vivo* permeation rate of the sheep buccal mucosa was shown to be significantly ($p < .05$) higher for MZ-SO NLC (1472 µg/cm^2) as compared with a marketed MZ formulation (1215 µg/cm^2) and an aqueous MZ suspension (470 µg/cm^2). Additionally, an *in vivo* efficacy study in terms of the ulcer index against *C. albicans* found a superior result for the optimized MZ-SO NLC (0.5 ± 0.50) in a treated group of animals. Hence, it can be concluded that MZ, through an optimized NLC of SO, can treat candidiasis effectively by inhibiting the growth of *C. albicans*.

Ameeduz Zafar *et al.*, (2020) this article provide information related developement and optimization of dapagliflozin loaded nanostructured lipid carriers (DG-NLCs) for the improvement of oral delivery. DG-NLCs were prepared by a high-pressure homogenization method (hot) and optimized by Box-Behnken design software using lipid, surfactant, and homogenization cycle as an independent variable. DG-NLCs were evaluated for particle size (Y1), entrapment efficiency (Y2), drug release (Y3). The DG-NLCs were further evaluated for morphology, thermal and X-ray diffraction analysis, ex-vivo intestinal permeation, and stability study. Particle size (nm), entrapment efficiency (%) and drug release (%) of all seventeen formulations were found in the range of 113.71-356.22 nm, 60.43-96.54% and 63.44-83.62% respectively. Morphology of optimized formulation exhibited spherical in shape confirmed by transmission electron microscopy. Thermal and X-ray diffraction analysis of NLCs showed the drug was solubilized and lost the crystallinity. DG-NLCs-opt exhibited dual release pattern initial fast and later sustained-release (90.01±2.01% in 24 h) whereas DG-

dispersion showed 31.54±1.87% release in 24 h. Korsmeyer-Peppas model was found to be the best fit model (R2 =0.999). The DG-NLCs-opt exhibited significant-high ($p < 0.05$, 1.293 µg/cm2 /h) flux than DG-dispersion (0.2683 µg/cm2 /h). Apparent permeation coefficient of DG-NLCs-opt was found to be significantly higher ($p < 0.05$, 4.14×10–5 cm/min) than DG dispersion (8.61×10–6 cm/min). The formulation showed no significant changes ($p < 0.05$) on six months of storage study at 25±2℃/60±5%RH. The finding concluded that quality by design (QbD) based lipid nanocarrier for oral delivery could be a promising approach of dapagliflozin for the management of diabetes.

Ahmed Gardouh *et al.*, (2019) this work related to preparation of tolnaftate loaded nanostructured lipid carriers via high shear homogenization method using solid lipid (Naterol GMS®) and liquid lipids (Dermarol CCT® and Dermarol DCO®) in the presence of non-ionic surfactants (Tween 80® and Span 20®) and Lecithin as co-surfactant. The optimum NLCs particle size formulae were loaded with tolnaftate, the particle size, zeta potential, polydispersity, TEM, DCS and *in vitro* release kinetics were investigated. The antifungal activity of the two formulas of tolnaftate showed no significant difference in antifungal activity and MIC. *In vitro* release results indicated that formula (NLC 45R) was the best formula as it showed the most delayed release pattern of drug. Formula (NLC 45R) showed drug release pattern followed Higuchi kinetic model. The results of the master sizer, TEM and Zetasizer confirmed that particles are in nano-size range.

Roohollah Mohseni *et al.*, (2019) this present article covers development of resveratrol (RES)-loaded solid lipid nanoparticle (SLN-RES) in order to improve insulin resistance through the up-regulation of SNARE protein complex in rats with type 2 diabetes. The SLN-RES characteristics include: the average size of 248 nm, the zeta potential of − 16.5 mV, and 79.9% RES entrapment efficiency. The release profile of SLN-RES showed an initial burst followed by a sustained release in natural condition. Infrared spectroscopy results revealed good incorporation of RES into core SLN. Spherical nanoparticle with less aggregation was observed under electronic microscopic examination. Oral administration of SLN-RES prevented weight loss and showed better hypoglycemic effect than RES. Serum oxidative stress status was restored to the normal level by SLN-RES. Furthermore, expression of synaptosomal-associated protein 23 (Snap23), syntaxin-4 (Stx4), and vesicle-associated membrane protein 2 (Vamp2) as the major elements of SNARE protein complex were

reduced by SLN-RES more significantly than RES treatment in muscle tissue. However, SLN-RES has a similar effect to RES treatment in adipose tissue. Taken together, our results revealed SLN-RES could be a modern and interestingly therapeutic approach for the improvement of insulin resistance through targeting the expression of Snap23, Stx4, and Vamp2 in adipose and muscle tissues.

Juntao Yin *et al.*, (2017) this article provide information related development of selenium-coated nanostructured lipid carriers (SeNLCs) for enhancing the oral bioavailability and the curative effect of berberine, an antidiabetic phytomedicine. Berberine-loaded SeNLCs (BB-SeNLCs) were prepared by hot-melt dispersion/homogenization procedure followed by in situ reduction. BB-SeNLCs were characterized by particle size, morphology, entrapment efficiency (EE) and in vitro release. Pharmacokinetics of berberine solution, berberine-loaded NLCs (BB-NLCs) and BB-SeNLCs were studied in Sprague Dawley rats administered by oral gavage. The prepared BB-SeNLCs were around 160 nm in particle size with an EE of 90%. In addition, BB-SeNLCs exhibited a better sustained release of berberine compared to the plain NLCs. After oral administration, BB-SeNLCs greatly enhanced the oral bioavailability of berberine, which was approximately 6.63 times as much as that of berberine solution. The hypoglycemic effect of BB-SeNLCs was also significantly superior to that of BB-NLCs and berberine solution. It turned out that sustained drug release and good intestinal absorption, plus the synergy of selenium, was basically responsible for enhanced oral bioavailability and hypoglycemic effect. Findings show that SeNLCs are promising nanocarriers for oral delivery of berberine to strengthen the antidiabetic action.

Andres Felipe Cartagena *et al*., (2017) this article gives information related to development preparations and evaluation Eudragit® L100 and Gantrez MS-955 microparticles containing miconazole nitrate for oral delivery. Microparticles were prepared by spray-drying method to achieve high encapsulation efficiency and increase the drug solubility. The microparticles were formed containing 10% and 20% of drug on polymer Eudragit® L100 (E10 and E20), Gantrez MS-955 (G10 and G 20) or their combination (EG10 and EG20). The influence of formulation factors (polymer:drug ratio, type of polymer) on yield percent, encapsulation efficiency, particle size, Fourier-transformed infrared spectroscopy (FTIR), X-ray diffraction, differential scanning calorimetry, in vitro drug release and antifungal activity were investigated. Acceptable yield, micrometer-sized and drug-loading efficiencies higher than

89% were obtained. No change in FTIR assignments was recorded after the microencapsulation procedure. X-ray and differential scanning calorimetry studies revealed amorphous/non-crystalline formulations. Miconazole nitrate-microparticles provided a remarkable increase of dissolution rate of the drug. Miconazole nitrate and G10, G20 and EG20 microparticles fitted to biexponential kinetic model, and E10, E20 and EG10 microparticles, monoexponential kinetic model. The antifungal activity test demonstrated that miconazole nitrate-microparticles possessed the same anti-Candida albicans activity as the pure drug. These results indicate that miconazole nitrate-microparticles are feasible carriers for increased release of miconazole at oral environment.

Feng Shi *et al.*, (2016) successfully prepared B-NLCs with high EE using high-pressure homogenization method. The results revealed that B-NLCs particles were uniformly in the nanosize range and of spherical morphology with a mean size of 92 ± 3.1 nm, a ZP of −31.35 ± 3.08 mV, and an EE of 85.29 ± 3.42%. Baicalin was released from NLCs in a sustained manner. In addition, B-NLCs showed a significantly higher antidiabetic efficacy compared with baicalin. The results indicated that B-NLCs possess relatively good physical stability and have a better ability to retain drugs. Furthermore, the NLCs formulation increased the antidiabetic efficacy of baicalin. Taken together, the NLCs developed in this study demonstrate a promising carrier for baicalin.

A I Mendes *et al.*, (2013) this article involves preparation and characterization of miconazole-loaded nanostructured lipid carriers (NLC) dispersion. Further, the dispersion was used to prepare a NLC-based hydrogel formulation proposed as an alternative system to improve the local delivery of miconazole to the oral mucosa. NLC dispersion showed particles in the nanometer range (≈ 200 nm) with low polidispersity index (<0.3), good physical stability and high encapsulation efficiency (>87%). A controlled miconazole release was observed from NLC and NLC-based hydrogel formulations, in contrast to a commercial oral gel formulation, which demonstrated a faster release. Additionally, it was observed that the encapsulation of miconazole in the NLC improved its antifungal activity against Candida albicans. It was demonstrated that the encapsulation of miconazole in NLC allows for obtaining the same therapeutic effect of a commercial oral gel formulation, using a 17-fold lower dose of miconazole.

4. Objectives of Research/ Proposed Hypothesis:

Aim: "Formulation, development and evaluation of Nanostructured Lipid Carrier for oral drug delivery system"

Objectives:

- To formulate, optimize and characterize drug-loaded nanostructured lipid carrier.
- To improve the efficacy, drug loading capacity and biocompatibility of poorly soluble drug by formulating in nanostructured lipid carrier.
- To reduce the toxicity and increase the stability of drug by encapsulating nanostructured lipid carrier.
- To improve drug incorporation & enhance bioavailability.
- To perform In-vitro study of nanostructured lipid carrier.
- To perform stability study of optimized nanostructured lipid carrier.
- To formulate & evaluate oral dosage form of optimized NLC.
- To perform In-vitro studies of formulation.
- To evaluate In-vivo bioavailability of drug from formulation in comparison with pure drug in experimental animal.
- To study the tissue distribution of drug from formulation in comparison with pure drug in experimental animal.
- To perform stability studies of optimized formulation.

5. Materials and Methodology to be adopted:

1. **Literature review**
2. **Selection and Collection of drug & excipients**
    - Selection of antidibetic / antifungal drug etc.
    - Selection of a lipid: To formulate the nanostructured lipid carrier, any of the following lipid will be selected.
      e.g. Castor oil or cholesterol or oleic acid etc.
3. **Experimental work**

A. Characterization of drug and excipients

- Spectroscopic studies
- Solubility studies

- Crystallinity studies

B. Compatibility studies

4. Formulation development

- Preparation of Nanostructured lipid carrier by using suitable method.

5. Characterization of drug-loaded Nanostructured lipid carrier

- Yield and drug content
- Particle size and zeta potential
- Encapsulation efficiency
- Surface morphology
- Fourier transform infrared spectroscopy
- XRD study
- Differential scanning colorimetry
- In vitro drug release
- Stability studies

6. Formulation & evaluation of oral dosage form of optimized NLCs.

7. In-vivo study

8. Stability studies.

6. Importance of study/ Society application:

- **International status:**

In pharmaceutical field, many drugs are being invented to combat the existing new diseases. The winds of change in the drug scenario are blowing forcefully worldwide. The emergence of new technologies provides an unique opportunities to exploit novel approaches in drug delivery. A shift from conventional drug delivery to novel drug delivery is noticed as conventional drug delivery suffers from various drawbacks, like most of the drugs that are available therapeutically come under BCS class II i.e, poorly soluble and high lipophilc. To assure progress in drug therapy, the development of new drugs merely is not sufficient. Issues arising in delivery of new drugs should also be addressed. Thus there is an emergent need to improve the bioavailability of these drugs, the only remedy or boon for such drugs is the discovery of some smart technologies which can

improve the bioavailability of these drugs. Nano drug delivery systems are the one such universal approach which fulfills the lacuna of conventional drug delivery systems. These Nano drug delivery systems, improves the pharmacokinetic profiles of many drugs. Nanotechnology is very helpful in diseases like diabetes, mycosis and cancer where there are many challenges. Worldwide there is increasing number of patients with diabetes, mycosis, and cancer. Most of the studies in last few years with nanostructured lipid carriers showed a promising result and accordingly there is an increasing number of patents on nano drug delivery in treatment of these diseases.

- **National status:**

  Indian peoples are suffering from various diseases like diabetes, mycosis, and cancer due to sedentary life style, poor living standard, improper diet, pollution, lack of awareness on these diseases, lack of early signs and symptoms etc. A big issue in India is lack of availability of most effective, safe and economic drug delivery for these diseases. Conventional formulations are available but these formulations have poor bioavailability and shows different side effects. Nanostructured lipid carriers have the potential to overcome the challenges related to various diseases. There is immense opportunity in India to develop a drug delivery with improved efficacy, biocompatibility, biodistribution and minimized toxicity in treatment of such diseases using NLCs.

►Significance of the study:

Different types of conventional drug delivery systems are there but this conventional drug delivery has various issues like poor bioavailability from target site, poor solubility, less therapeutic effect etc. Drug bioavailability is directly related to its ability to dissolve, transport and/or absorb through the physiological environment. A great number of drugs are characterized with low water solubility due to their hydrophobic nature, thus limiting their oral bioavailability and clinical use. Therefore, new strategies aiming to provide a protective shell through the GI system and improve drug solubility and permeability in the intestine were developed to overcome this limitation. These problems can be resolved by nanotechnology since it exploits the unique properties of materials at the nanoscale. Nanotechnology has gained popularity in several industries, as it offers better built and smarter products. Nanostructured lipid carriers (NLCs) are drug-delivery systems composed of both solid and liquid lipids as a core matrix. It was shown that NLCs reveal some advantages for drug

therapy over conventional carriers including increased solubility, the ability to enhance storage stability, improved permeability and bioavailability, reduced adverse effect, prolonged half-life, and tissue-targeted delivery. NLCs have attracted increasing attention in recent years. The application of nanotechnology in medicine and healthcare is referred to as nanomedicine and it has been used to fight various diseases. Lipid-based systems have been proposed as good candidates for drug delivery owing to their hydrophobic nature which allows high drug loading, drug micellization ability during intestinal digestion due to the lipid content and the vehicle physical protective environment. Hence it is need of hour to develop a formulation of the nanostructured lipid carrier for oral drug delivery system.

7. Proposed work Plan/ Formulation and Structure of Study:

Year-wise Plan of work and targets to be achieved:

<table>
<tr><th>Sr. No.</th><th>Expected target to be achieved</th><th>1-6 Months</th><th>7-10 Months</th><th>11-22 Months</th><th>22- 27 Months</th><th>28 -33 Months</th><th>34-36 Months</th></tr>
<tr><td>01</td><td>Literature survey</td><td>Literature survey</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>02</td><td>Selection and collection of drug and excipients</td><td colspan="2">Selection and collection of drug and excipients</td><td></td><td></td><td></td><td></td></tr>
<tr><td>03</td><td>Formulation, development and optimization of NLCs & oral dosage form</td><td colspan="3">Formulation, development and optimization of NLCs & oral dosage form</td><td></td><td></td><td></td></tr>
<tr><td>04</td><td>Evaluation of nanostructured lipid carrier</td><td colspan="4">Evaluation of nanostructured lipid carrier</td><td></td><td></td></tr>
<tr><td>05</td><td>In-vitro, In-vivo & stability study</td><td colspan="5">In-vitro, In-vivo & stability study</td><td></td></tr>
<tr><td>06</td><td>Statistical Analysis, Data Interpretation and Conclusions</td><td colspan="6">Statistical Analysis, Data Interpretation and Conclusions</td></tr>
<tr><td>07</td><td>Publishing Research and submitting data</td><td colspan="6">Publishing Research and submitting data</td></tr>
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